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EXAMINER	
JIANG, SHAOJIA A	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,449	SZELENYI ET AL.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on August 31, 2004 wherein claims 1-8 have been amended.

Currently, claims 1-8 are pending in this application.

Claims 1-8 as amended now are examined on the merits herein.

The copy of certified copy, German 199 47 235.1, for the priority under 35 U.S.C. 119(a)-(d) has been filed September 13, 2004. It is noted that German 199 47 235.1 is in Germany, no translation into English is provided.

Applicant's amendment filed August 31, 2004 with respect to the rejection of claims 1-8 made under 35 U.S.C. 112 second paragraph for the use of the indefinite recitations, i.e., "tolerable" and "customary excipient" in the claims of record stated in the Office Action dated February 24, 2004 have been fully considered and found persuasive to remove the rejection since these indefinite recitations have been deleted from the claims. Therefore, the said rejection is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 7-8 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular β2 adrenoceptor agonist, such as salbutnmol, reproterol, salmeterol, and formoterol disclosed in the specification herein, does not reasonably provide enablement for any β2 adrenoceptor agonists employed in the pharmaceutical composition and the particular method of treatment for asthma or allergy recited in the claims herein, for the same reasons of record stated in the Office Action dated February 24, 2004.

These recitation, "one β2 adrenoceptor agonist", is seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a pharmaceutical composition and the particular method of treatment for asthma or allergy.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims read on any compounds having function as β2 adrenoceptor agonist.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

In the instant case, "one β2 adrenoceptor agonist", recited in the instant claims is purely functional distinction. Hence, the functional recitation reads on any compounds that might have the recited functions. However, the specification merely provides four particular compound for this functional compounds for the composition and particular method herein.

Thus, Applicants functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a

human) the ***combination*** of any compounds represented by "one β2 adrenoceptor agonist", and loteprednol, which may encompass more than a thousand compounds. See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added). In the instant case, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having claimed functional properties in the pharmaceutical compositions herein to be administered to a host. Thus, the teachings of the book clearly support that the instant claimed invention is highly unpredictable.

The presence or absence of working examples and the quantity of experimentation necessary:

It is noted that only four particular adrenergic β2 receptor agonists, salbutnmol, reproterol, salmeterol, and formoterol, in combination with loteprednol employed in the composition herein are shown in the working examples of the specification herein. Thus,

the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the active agents or compounds in the claimed composition. See MPEP § 716.02(d).

Thus, the specification fails to provide sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having the function recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims and their combinations employed in the claimed compositions to be administered to a host, with no assurance of success.

Response to Argument

Applicant's arguments filed August 31, 2004 with respect to this rejection made under 35 U.S.C. 112, first paragraph, for scope of enablement of record in the previous

Office Action February 24, 2004 have been fully considered but are not deemed persuasive as further discussed below.

Applicant arguments that "[T]he whole group of β2-adrenoreceptor agonists is known to bind very specifically only to β2-adrenoreceptors which are expressed in bronchial and smooth muscle tissue. This biological activity is in contrast to the expression of β1-adrenoreceptors, which occurs mainly in cardiac tissue", have been considered but not found convincing.

First, the recitation, "one β2 adrenoceptor agonist" may reasonably encompass not only those known but also unknown β2 adrenoceptor agonists as of the instant filing date, even those future known β2 adrenoceptor agonists. Note those **future known** compounds yet to be discovered and/or made. Hence, those unknown or future known compounds broadly encompassed by the claims herein must require to additional or future research to discover, establish or verify their usefulness. Therefore, as indicated in the previous Office Action, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

Second, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would not be able to fully predict therapeutic effects, side effects, and possible adverse drug-drug interactions occurring with any combinations of any compounds represented by "one β2 adrenoceptor agonist", and loteprednol, according to the book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996). Thus, again, to

practice the claimed invention herein, a person of skill in the art would have to exercise **undue experimentation** to test any combinations encompassed by the claims herein.

Third, Applicant argues that β2 adrenoceptor agonists all share specific structural features. However, claims 1-2 and 7-8 are **not** limited to any specific structural features.

For the above stated reasons, said claims are properly rejected made under 35 U.S.C. 112, first paragraph, for lack of full scope of enablement.

The following is new rejection(s) necessitated by Applicant's amendment filed on August 31, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "pharmaceutically effective ester" in the instant claim renders claim 1 indefinite. One of ordinary skill in the art would acknowledge that there are two moieties for loteprenol ester such as loteprenol and etabonate. Since the recitation "pharmaceutically effective ester" is not clearly defined in the claims and specification, one of ordinary skill in the art could not interpret the metes and bounds of the patent

protection desired as to the other moiety of loteprenol ester encompassed thereby, except for loteprenol etabonate.

Given the fact that any significant structural variation to a compound would be reasonably expected to alter its properties, e.g., physical, chemical, physiological effects and functions. Thus, it is unclear and indefinite as to the "pharmaceutically effective ester" of loteprenol herein encompassed thereby.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over DOI, Koji (WO 9831343) and BJERKEC and van der Molen for the same reasons of record stated in the Office Action dated February 24, 2004.

Doi discloses that loteprednol etabonate is known to be useful in a pharmaceutical composition and a method of treating inflammatory conditions or allergy since loteprednol etabonate has excellent anti inflammatory and antiallergic activities and is value as a drug in an ointment or a liquid form, and loteprednol etabonate is formulated into a long-term stable liquid suspension for nasal administration (see abstract, page 1, 1st and 2nd paragraphs, Examples at page 7-11, calims 1-5).

According to Bjerkec, long-acting β2 agonists, for example, salmeterol and formoterol, are bronchospasmolytics, are used as inhalations in asthma treatment. These long-acting β2 agonists should always be given in combination with corticosteroids. Short-acting β2 agonists, for example, salbutamol, may be given additionally (see abstract; page 587 'Introduction'; page 589, right-hand column, paragraph 4; page 590 'Conclusion'). The corticosteroids indicated include beclomethasone dipropionate, budesonide and fluticasone propionate (see page 588, left-hand column, lïnes 1-2; page 589, right-hand column, line 19).

The clinical study described in van der Molen shows that the symptoms of asthma patients are improved on inhalation of the long-acting β2 agonist, formoterol in addition to inhaled corticosteroids (see abstract; page 536 'Subjects'; page 538 'Discussion'). Van der Molen does not specify the corticosteroids used.

The prior art does not expressly disclose that the employment of loteprednol etabonate in combination with reproterol, salmeterol, or formoterol in a pharmaceutical composition and a method for the treatment of allergies and/or airway disorders for simultaneous, sequential or separate administration.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ loteprednol etabonate in combination with reproterol, salmeterol, or formoterol in a pharmaceutical composition and a method for the treatment of allergies and/or airway disorders for simultaneous, sequential or separate administration.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ loteprednol etabonate in combination with reproterol, salmeterol, or formoterol in a pharmaceutical composition and a method for the treatment of allergies and/or airway disorders for simultaneous, sequential or separate administration, since both loteprednol etabonate, and reproterol, salmeterol, or formoterol, are known to be useful in a pharmaceutical composition and a method for the treatment of allergies and/or airway disorders such as asthma based on the prior art.

Therefore, one of ordinary skill in the art would have reasonably expected that combining loteprednol etabonate and reproterol, salmeterol, or formoterol both known useful for the same purpose, i.e., treating allergies and/or airway disorders such as asthma, would improve the therapeutic effects for treating the same diseases, and/or would produce additive therapeutic effects in treating the same.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Moreover, the teachings of Bjerkec and van der Molen have further clearly provided the motivation for the instant combination, because long-acting β2 agonists, should always be given in combination with corticosteroids according to Bjerkec. The clinical study described in van der Molen shows that the symptoms of asthma patients

are improved on inhalation of the long-acting β2 agonist, formoterol in addition to inhaled corticosteroids. It is noted that loteprednol etabonate is the particular corticosteroid.

Further, the process for preparation of a pharmaceutical composition herein is considered well within conventional skills in pharmaceutical science.

Thus the claimed invention as a whole is seen prima facie obvious over the combined teachings of the prior art.

Response to Argument

Applicant's arguments filed August 31, 2004 with respect to this rejection under 35 U.S.C. 103(a) of record in the previous Office Action February 24, 2004 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicant's assertion that "the cited references as discussed below fail to recite all of the elements of the presently claimed invention and fail to provide an expectation of success or motivation to arrive at the claimed invention" has been considered but is not found persuasive.

One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 SPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145. More importantly, it has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form a third composition that is to be used for the

very same purpose; idea of combining them flows logically from their having been individually taught in prior art. *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

In the instant case, as discussed in the previous Office Action, one having ordinary skill in the art at the time the invention was made would have been motivated to employ loteprednol etabonate in combination with reproterol, salmeterol, or formoterol in a pharmaceutical composition and a method for the treatment of allergies and/or airway disorders for simultaneous, sequential or separate administration, since both loteprednol etabonate, and reproterol, salmeterol, or formoterol, are known to be useful in a pharmaceutical composition and a method for the treatment of allergies and/or airway disorders such as asthma based on the prior art.

Therefore, one of ordinary skill in the art would have reasonably expected that combining loteprednol etabonate and reproterol, salmeterol, or formoterol both known useful for the same purpose, i.e., treating allergies and/or airway disorders such as asthma, would improve the therapeutic effects for treating the same diseases, and/or would produce additive therapeutic effects in treating the same.

Since all active composition components herein are known to useful to treat cancer, it is considered prima facie obvious to combine them into a single composition to form a third composition useful for the very same purpose. At least additive therapeutic effects would have been reasonably expected based on the well settled principle set forth *In re Kerkhoven* regarding combination inventions. Therefore,

motivation to combine the teachings of the prior art cited herein to make the present invention is seen. The claimed invention is obvious in view of the prior art.

Applicant's assertion in regard to unexpected results, and testing data shown in the Table 1-2 of the specification at pages 5-6 herein have been fully considered but are not deemed persuasive as to the nonobviousness and/or unexpected results of the claimed invention over the prior art. Table 1-2 herein merely demonstrate tow particular combinations within the instant claims, i.e., salbutamol and loteprednol; formoterol and loteprednol. Thus, the evidence in the examples is also not commensurate in scope with the claimed invention, and does not demonstrate criticality of a claimed range of the ingredients in the claimed composition, i.e., any β2 adrenoceptor agonist in combination with any ester of loteprednol. See MPEP § 716.02(d).

Moreover, the results on the tests of the employment of salbutamol and loteprednol; formoterol and loteprednol would be expected according to the teachings of Bjerkec and van der Molen, because long-acting β2 agonists, should always be given in combination with corticosteroids according to Bjerkec. The clinical study described in van der Molen shows that the symptoms of asthma patients are improved on inhalation of the long-acting β2 agonist, formoterol in addition to inhaled corticosteroids. It is noted that loteprednol etabonate is the particular corticosteroid. Note that expected beneficial results are evidence of obviousness. See MPEP § 716.02(c).

Therefore, the evidence presented in specification herein is not seen to be clear and convincing in support the nonobviousness of the instant claimed invention over the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9307.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner, AU 1617
November 8, 2004